



Docket No.: 22116-00005-US3

(PATENT)

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In re Patent Application of:
Nicolaas M.J. Vermeulin, et al

Application No.: 09/396,523

Group Art Unit: 1621

Filed: September 15, 1999

Examiner: Peter G. O'Sullivan

For: POLYAMINE ANALOGUES AS
THERAPEUTIC AND DIAGNOSTIC AGENTS

RESPONSE

Commissioner for Patents
Washington, DC 20231

Dear Sir:

This is in response to the Office Action mailed October 22, 2002.

Claims 3 and 32-53 are now in the application. Claims 3, 33-48 and 53 are drawn to the elected invention. Claims 32 and 49-52 are drawn to non-elected invention and may be cancelled by the Examiner upon the allowance of the claims directed to the elected invention.

The provisional rejection of claims 3, 33, 34, 35-48 and 53 under the judicially created doctrine of obviousness type double patenting as being unpatentable over the claims of copending application S.N. 09/713,512 will be overcome by the filing of a terminal disclaimer. Such will be filed upon overcoming the remaining rejections in the cases. The filing of a terminal disclaimer is not to be construed as an admission, estoppel or acquiescence. See *Quad Environmental Technology v. Union Sanitary District*, 20 USPQ2d 1392 (Fed. Cir. 1991) and *Ortho Pharmaceuticals Corp. v. Smith*, 22 USPQ2d 1119 (Fed. Cir. 1992).

The rejection of claims 3, 33 and 34 under 35 USC 103(a) as being unpatentable over

Cherksey is not deemed tenable. Cherksey does not render obvious claims 3, 33 and 34 since, among other things, Cherksey does not disclose the claimed stereoisomeric form of the claimed compounds, and does not lead one skilled in the art to select the claimed stereoisomers as possessing the beneficial results. As recognized by the Examiner, applicants have provided a showing of beneficial results for the claimed stereoisomers (see page 3, lines 3 and 4 of the Office Action). However, the rejection of claims 3, 33 and 34 was maintained based upon the incorrect premise that "it is expected that there will be differences in activity of various stereoisomers in biological systems", and the reliance upon *In re Adamson*, 125 USPQ 233 and *In re May*, 197 USPQ 601.

Even if the above conclusory statement were accurate, which it is not, the claims are still patentable since the cited art does not suggest which of the stereoisomers would possess the better properties. The statement is merely an invitation to experiment. Accordingly, the rejection is in the nature of the impermissible standard of "ought to be tried". See *Jones v. Hardy*, 220 USPQ 1021 (Fed. Cir. 1984).

The degree of differential activity exhibited by stereoisomers of biological molecules is extremely variable and must be determined empirically. In fact, many enzymes will show marked stereospecificity for one class of inhibitors, while not distinguishing between enantiomers of another class. For example, the four stereoisomers of alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid, all bind and inhibit carboxypeptidase A with similar inhibition constants. Chung *et al.*, *J. Org. Chem.* 66:6462-71 (2001). However, the D-configuration of another carboxypeptidase A inhibitor, N-Hydroxyaminocarbonyl)phenylalanine, binds the enzyme three times tighter than the corresponding L-configuration. Chung and Kim, *Bioorg. Med. Chem.* 9: 185-9 (2001). Generally, it has been suggested that inhibitors of an enzyme's ground state may show marked stereospecificity, where irreversible and mechanism based inhibitors may show little or no stereospecificity. Kim, D.H., *Mini Rev. Med. Chem.* 1:155-61 (2001). Accordingly, the potential degree of stereospecificity that may be demonstrated by the claimed compounds cannot be predicted.

The cases relied upon by the Examiner do not suggest otherwise. For instance, *In re May* found the claims rejected under 35 USC 103 to be patentable. Only the claims that were anticipated stood the test of unpatentability under 35 USC 102.

The earlier case relied upon, *In re Adamson*, involved a rejection based on a combination of at least two references. If anything it is at odds with *In re May*, as well as with *In re Williams*, 80 USPQ 150 which was cited with approval in *In re May*. In *Williams*, the Court stated that the novelty of an optical isomer is not negated by prior art disclosure of the racemate.

Furthermore, *In re Adamson* differs from the present situation. In particular, the facts of *Adamson* involved differences in the same activity between the L- and O- forms of a compound. In the present case, differences in a different activity (tissue accumulation) as well as an additional activity (polyamine transport inhibition) have been shown.

Also, the rejection fails to take into account more recent case law concerning 35 USC 103 as enunciated by the Federal Circuit.

Also see *In re Nathan*, 140 USPQ 601 (CCPA 1964) and *In re Magerlein*, 145 USPQ 683 (CCPA 1965) which, although involving a different issue, illustrate the patentability of claims directed to specific stereoisomers of a prior art compound.

The rejection is also inconsistent with the plethora of issued patents directed to specific stereoisomers of prior art compounds. See, for instance, U.S.P. 4,871,852 (copy attached).

Also, the mere fact that cited art may be modified in the manner suggested by the Examiner does not make this modification obvious, unless the cited art suggest the desirability of the modification. No such suggestion appears in the cited art in this matter. The Examiner's attention is kindly directed to *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), *In re Dembicza et al.* 50 USPQ2d. 1614 (Fed. Cir. 1999), *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984), *In re Laskowski*, 10 USPQ2d. 1397 (Fed. Cir. 1989) and *In re Fritch*, 23, USPQ2d. 1780 (Fed. Cir. 1992).

In *Dembiczak et al.*, *supra*, the Court at 1617 stated: "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., C.R. Bard, Inc., v. M3 Sys., Inc., 157 F.3d. 1340, 1352, 48 USPQ2d. 1225, 1232 (Fed. Cir. 1998) (describing 'teaching or suggestion motivation [to combine]' as in 'essential evidentiary component of an obviousness holding'), In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d. 1453, 1459 (Fed. Cir. 1998) ('the Board must identify specifically...the reasons one of ordinary skill in the art would have been motivated to select the references and combine them');...".

Also, the cited art lacks the necessary direction or incentive to those of ordinary skill in the art to render a rejection under 35 USC 103 sustainable. The cited art fails to provide the degree of predictability of success of achieving the properties attainable by the present invention needed to sustain a rejection under 35 USC 103. See *Diversitech Corp. v. Century Steps, Inc.* 7 USPQ2d 1315 (Fed. Cir. 1988), *In re Mercier*, 185 USPQ 774 (CCPA 1975) and *In re Naylor*, 152 USPQ 106 (CCPA 1966).

Moreover, the properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 USC 103. See *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d. 1923 (Fed. Cir. 1990), *In re Antonie*, 195, USPQ 6 (CCPA 1977), *In re Estes*, 164 USPQ (CCPA 1970), and *In re Papesch*, 137 USPQ 43 (CCPA 1963).

No property can be ignored in determining patentability and comparing the claimed invention to the cited art. Along these lines, see *In re Papesch*, *supra*, *In re Burt et al*, 148 USPQ 548 (CCPA 1966), *In re Ward*, 141 USPQ 227 (CCPA 1964), and *In re Cescon*, 177 USPQ 264 (CCPA 1973).

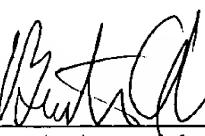
In view of the above, consideration and allowance are, therefore, respectfully solicited.

In the event that the Examiner believes an interview might serve to advance the prosecution of this application in any way, the undersigned attorney is available at the telephone number noted below.

The Commissioner is hereby authorized to charge any fees or credit any overpayment associated with this communication including any extension fees to Deposit Account No. 22-0185.

Dated: February 24, 2003

Respectfully submitted,

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